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**SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR  
TREATMENT OF MEDICAL DISORDERS**

10 This application is a continuation-in-part of application USSN 90/373,828, filed  
August 13, 1999, which claims the benefit of U.S. provisional patent application USSN  
60/130,074, filed April 19, 1999; U.S. provisional patent application USSN 60/134,320,  
filed May 14, 1999; U.S. provisional patent application USSN 60/143,959, filed July 15,  
1999; U.S. provisional patent application USSN 60/148,234, filed August 11, 1999; U.S.  
provisional patent application USSN 60/164,676, filed November 10, 1999; and U.S.  
15 provisional patent application USSN 60/184,864, filed February 25, 2000.

**FIELD OF THE INVENTION**

The invention pertains to methods for treating various medical disorders that are  
characterized by abnormal or excessive TNF $\alpha$  levels by administering a TNF $\alpha$   
antagonist, preferably a soluble TNF $\alpha$ . The TNF $\alpha$  inhibitor may be administered in  
20 combination with other biologically active molecules.

**BACKGROUND OF THE INVENTION**

The pleiotropic cytokine tumor necrosis factor alpha (TNF $\alpha$ ) is associated with  
inflammation and binds to cells through membrane receptor molecules, including two  
molecules having molecular weights of approximately 55 kDa and 75 kDa (p55 and p75).  
25 In addition to binding TNF $\alpha$ , the p55 and p75 TNF receptors mediate the binding to cells  
of homotrimers of TNF $\beta$ , which is another cytokine associated with inflammation and  
which shares structural similarities with TNF $\alpha$  (e.g., see Cosman, *Blood Cell Biochem*  
7:51-77, 1996). TNF $\beta$  is also known as lymphotoxin- $\alpha$  (LT $\alpha$ ).

It has been proposed that a systemic or localized excess of TNF $\alpha$  contributes to  
30 the progression of numerous medical disorders. For example, patients with chronic heart  
failure have elevated levels of serum TNF $\alpha$ , which have been shown to increase with  
disease progression (see, for example, Levine et al., *N Eng J Med* 323:236-241, 1990). A  
variety of other diseases are associated with elevated levels of TNF $\alpha$  (see, for example,  
Feldman et al., *Transplantation Proceedings* 30:4126-4127, 1998).

35 Psoriatic arthritis (PsA) is a chronic autoimmune condition that shares some  
features with both rheumatoid arthritis (RA) and the inflammatory skin disease psoriasis  
(for review, see Breathnach, In Klippel and Dieppe eds. *Rheumatology*, 2<sup>nd</sup> Ed., Mosby,

1998, 22.1-22.4). Psoriasis is characterized by epidermal keratinocyte hyperproliferation, accompanied by neutrophil and T cell infiltration, and is associated with elevated levels of inflammatory cytokines, including TNF $\alpha$ , IL-6 and TGF $\beta$  (see, for example, Bonifati et al., *Clin Exp Dermatol* 19:383-387, 1994). Psoriasis and PsA are different clinical entities, and are associated with somewhat different MHC haplotypes (Gladman, *Rheum Dis Clin NA*. 18:247-256, 1992; Breathnach, 1998). The overall prognosis for PsA is far worse than for ordinary psoriasis. Nonetheless, treatments used for the psoriatic lesions of PsA generally are similar to those used to treat psoriasis.

Psoriatic skin lesions are present in patients with PsA, although only a minority of psoriasis sufferers actually have PsA. Ordinary psoriasis occasionally is accompanied by joint pain, but does not involve the extreme pain and often deforming degeneration of joints and bone that occurs in PsA patients.

Treatments that sometimes are effective in treating ordinary psoriasis include topical medications (e.g., steroids, coal tar, anthralin, Dead Sea salts, various natural oils, vitamin D3 and its analogs, sunshine, topical retinoids), phototherapy (e.g., ultraviolet light, photochemotherapy (PUVA)), and internal medications (e.g., methotrexate, systemic steroids, oral retinoids, cyclosporine, or a rotating regimen of these three). In addition, it has been proposed that psoriasis could be treated with TNF-derived peptides, quinolinesulfonamides, pyrrolidinone derivatives, catechol diether compounds, isoxazoline compounds, matrix metalloproteinase inhibitors or mercapto alkyl peptidyl compounds, all of which inhibit either TNF $\alpha$  production or its release from cultured cells (see, for example, U.S. 5,691,382, U.S. 5,834,485, U.S. 5,420,154, U.S. 5,563,143, U.S. 5,869,511 and U.S. 5,872,146), as well as with various combination therapies involving TNF $\alpha$  antagonists (for example, see U.S. 5,888,511 or U.S. 5,958,413).

Conflicting results have been reported regarding the role of TNF $\alpha$  in psoriasis. Some investigators have proposed that overproduction of TNF $\alpha$  contributes to the pathology of psoriasis (e.g., Pigatto et al., *J Invest Dermatol* 94:372-376, 1990; Sagawa et al., *Dermatol* 187:81-83, 1993; Ameglio et al., *Dermatol* 189:359-363, 1994). One group reported some improvement after treatment with pentoxifylline, a drug that can inhibit the release of TNF $\alpha$ , but which exerts many of its physiological effects by inhibiting cyclic AMP phosphodiesterase (Omulecki et al., *J Am Acad Dermatol* 34:714-715, 1996; Centola et al., *J Androl* 16:136-142, 1995; Elferinck et al., *Biochem Pharmacol* 54:475-480, 1997). However, other reports have cast doubt on the hypothesis that

5 overproduction of TNF $\alpha$  exacerbates psoriasis. For example, some investigators have reported that treatment with TNF $\alpha$  itself actually can mitigate psoriasis (see, e.g., Takematsu et al., *Br J Dermatol* 124:209-210, 1991; Creaven et al., *J Am Acad Dermatol* 24:735-737, 1991).

10 In addition to psoriatic lesions, PsA is characterized by distal interphalangeal joint (DIP) involvement, enthesopathy, nail lesions, spondylitis and dactylitis. The histopathogenesis of PsA and the more well-studied rheumatoid arthritis share certain features. In both RA and in active PsA, patients exhibit increased levels of HLA-DR<sup>+</sup> T cells and MHC class II antigens in their synovial membranes and synovial fluid, as well as increased expression of the cytokine TNF $\alpha$ . In addition, both diseases are associated  
15 with prominent synovial vascular changes.

The discovery of rheumatoid factor in the serum of RA patients provided an important tool for differentiating PsA from RA, but the realization that RA and PsA are distinct diseases was based primarily on their many clinical differences (e.g., Helliwell and Wright, *In Klippel and Dieppe eds. Rheumatology*, 2<sup>nd</sup> Ed., Mosby, 1998, 21.1-21.8).  
20 Studies have shown that levels of TNF $\alpha$ , IL-1 $\beta$ , IL-8 as well as TNF $\alpha$  receptors in synovial fluids were higher in PsA patients than in osteoarthritis patients, though they were lower than in RA patients (Parsch et al., *J Rheumatol* 24:518-523, 1997; Parsch et al., *J Rheumatol* 25:105-110, 1998; Parsch et al., *Ann Rheum Dis* 57:691-693, 1998). PsA is distinguished from RA also by radiographic appearance, a notably higher degree of  
25 synovial membrane vascularity as well as differences in the levels of various cytokines in the synovial fluids (Ritchlin et al., *J Rheumatol* 25:1544-52, 1998; Veale et al., *Arth Rheum* 36:893-900, 1993). Veale et al. noted differences in synovial membrane adhesion molecules and numbers of macrophages when they compared RA and PsA patients, as well as observing a minimal degree of hyperplasia and hypertrophy of synoviocytes in  
30 PsA as compared with RA patients. Because of such differences, coupled with the association of PsA but not RA with class I MHC antigens, Ritchlin et al. have suggested that PsA must be triggered by different mechanisms than those underlying RA. Veale et al. suggested for similar reasons that different cytokines were likely to be interacting in the synovium of PsA and RA patients.

35 Most of the drugs used for treating the arthritic aspects of PsA are similar to those used in RA (Salvarini et al., *Curr Opin Rheumatol* 10:229-305, 1998), for example the non-steroidal antiinflammatories (NSAIDs), which may be used alone or in combination

5 with the disease-modifying anti-rheumatic drugs, or "DMARDs." However, one group  
found that long-term administration of the DMARD methotrexate failed to slow the  
progression of joint damage in PsA patients (Abu-Shakra et al., *J Rheumatol* 22:241-45,  
1995), and another group reported very little improvement in PsA patients who had  
received methotrexate (Willkens et al., *Arthr Rheum* 27:376-381, 1984). Similarly, Clegg  
10 et al. found only a slight improvement over placebo in PsA patients treated with  
sulfasalazine, another drug classified as a DMARD (Clegg et al., *Arthritis Rheum* 39:  
2013-20, 1996). Some studies have indicated that the immunosuppressor cyclosporine is  
effective in treating PsA (reviewed in Salvarini et al., 1998), though this drug has severe  
side effects. In addition, others have proposed that PsA could be treated with truncated  
15 TNF $\alpha$  receptors or with a combination of methotrexate and antibodies against TNF $\alpha$   
(WO 98/01555; WO 98/0537).

A recent meta-analysis of a number of PsA treatment studies concluded that PsA  
and RA differed not only in their response to treatment with specific drugs, but in the  
relative magnitudes of improvement in the placebo arms of the studies (Jones et al., *Br J*  
20 *Rheumatol* 36:95-99, 1997). As an example, PsA patients responded better to gold salt  
therapy than did RA patients, though the gold did not affect the psoriatic skin lesions  
(Dorwart et al., *Arthritis Rheum* 21:515-513, 1978).

It has been suggested that the suppression of TNF $\alpha$  might be beneficial in patients  
suffering from various disorders characterized by abnormal or excessive TNF $\alpha$   
25 expression. However, although progress has been made in devising effective treatment  
for such diseases, improved medicaments and methods of treatment are needed.

### **SUMMARY OF THE INVENTION**

Provided herein are methods for treating a number of medical disorders  
30 characterized by abnormal TNF $\alpha$  expression by repeatedly administering an antagonist of  
TNF $\alpha$ , such as a soluble TNF $\alpha$  receptor, for a period of time sufficient to induce a  
sustained improvement in the patient's condition.

### **DETAILED DESCRIPTION OF THE INVENTION**

This invention provides compounds, compositions and methods for treating a  
35 mammalian patient, including a human patient, who is suffering from a medical disorder  
that is characterized by abnormal or elevated expression of TNF $\alpha$ . For purposes of this

5 disclosure, the terms “illness,” “disease,” “medical condition,” “abnormal condition” and the like are used interchangeably with the term “medical disorder.”

The subject methods involve administering to the patient a soluble TNF $\alpha$  antagonist that is capable of reducing the effective amount of endogenous biologically active TNF $\alpha$ , such as by reducing the amount of TNF $\alpha$  produced, or by preventing the  
10 binding of TNF $\alpha$  to its cell surface receptor (TNFR). Antagonists capable of inhibiting this binding include receptor-binding peptide fragments of TNF $\alpha$ , antibodies directed against TNF $\alpha$ , and recombinant proteins comprising all or portions of receptors for TNF $\alpha$  or modified variants thereof, including genetically-modified muteins, multimeric forms and sustained-release formulations. Other compounds suitable for treating the diseases  
15 described herein include thalidomide and pentoxifylline.

Preferred embodiments of the invention utilize soluble TNFRs as the TNF $\alpha$  antagonist. Soluble forms of TNFRs may include monomers, fusion proteins (also called “chimeric proteins), dimers, trimers or higher order multimers. In certain embodiments of the invention, the soluble TNFR derivative is one that mimics the 75 kDa TNFR or the  
20 55 kDa TNFR and that binds to TNF $\alpha$  in the patient’s body. The soluble TNFR mimics of the present invention may be derived from TNFRs p55 or p75 or fragments thereof. TNFRs other than p55 and p75 also are useful for deriving soluble compounds for treating the various medical disorders described herein, such for example the TNFR described in WO 99/04001. Soluble TNFR molecules used to construct TNFR mimics  
25 include, for example, analogs or fragments of native TNFRs having at least 20 amino acids, that lack the transmembrane region of the native TNFR, and that are capable of binding TNF $\alpha$ . Antagonists derived from TNFRs compete for TNF $\alpha$  with the receptors on the cell surface, thus inhibiting TNF $\alpha$  from binding to cells, thereby preventing it from manifesting its biological activities. Binding of soluble TNFRs to TNF $\alpha$  or LT $\alpha$  can be  
30 assayed using ELISA or any other convenient assay. This invention provides for the use of soluble TNF $\alpha$  receptors in the manufacture of medicaments for the treatment of numerous diseases.

The soluble TNFR polypeptides or fragments of the invention may be fused with a second polypeptide to form a chimeric protein. The second polypeptide may promote  
35 the spontaneous formation by the chimeric protein of a dimer, trimer or higher order muimer that is capable of binding a TNF $\alpha$  and/or LT $\alpha$  molecule and preventing it from binding to cell-bound receptors. Chimeric proteins used as antagonists include, for

5 example, molecules derived from an antibody molecule and a TNFR. Such molecules are referred to herein as TNFR-Ig fusion proteins. A preferred TNFR-Ig fusion protein suitable for treating diseases in humans and other mammals is recombinant TNFR:Fc, a term which as used herein refers to "etanercept," which is a dimer of two molecules of the extracellular portion of the p75 TNF $\alpha$  receptor, each molecule consisting of a 235 amino  
10 acid TNFR-derived polypeptide that is fused to a 232 amino acid Fc portion of human IgG<sub>1</sub>. Etanercept is currently sold by Immunex Corporation under the trade name ENBREL.<sup>®</sup> Because the p75 receptor protein that it incorporates binds not only to TNF $\alpha$ , but also to the inflammatory cytokine LT $\alpha$ , etanercept can act as a competitive inhibitor not only of TNF $\alpha$ , but also of LT $\alpha$ . This is in contrast to antibodies directed against  
15 TNF $\alpha$ , which cannot inhibit LT $\alpha$ . Also encompassed by the invention are treatments using a compound that comprises the extracellular portion of the 55 kDa TNFR fused to the Fc portion of IgG, as well as compositions and combinations containing such a molecule. Encompassed also are therapeutic methods involving the administration of TNFR-Ig proteins derived the extracellular regions of TNF $\alpha$  receptor molecules other  
20 than the p55 and p75 TNFRs, such as for example the TNFR described in WO 99/04001.

In one preferred embodiment of the invention, sustained-release forms of soluble TNFRs are used, including sustained-release forms of TNFR:Fc. Sustained-release forms suitable for use in the disclosed methods include, but are not limited to, TNFRs that are encapsulated in a slowly-dissolving biocompatible polymer (such as the alginate  
25 microparticles described in U.S. 6,036,978), admixed with such a polymer (including topically applied hydrogels), and or encased in a biocompatible semi-permeable implant. In addition, the soluble TNFR may be conjugated with polyethylene glycol (pegylated) to prolong its serum half-life or to enhance protein delivery.

In accord with this invention, medical disorders characterized by abnormal or  
30 excess expression of TNF $\alpha$  are administered a therapeutically effective amount of a TNF $\alpha$  inhibitor. The TNF $\alpha$  inhibitor may be a TNF $\alpha$ -binding soluble TNF $\alpha$  receptor, preferably TNFR:Fc. As used herein, the phrase "administering a therapeutically effective amount" of a therapeutic agent means that the patient is treated with the agent in an amount and for a time sufficient to induce a sustained improvement in at least one  
35 indicator that reflects the severity of the disorder. An improvement is considered "sustained" if the patient exhibits the improvement on at least two occasions separated by one or more weeks. The degree of improvement is determined based on signs or

5 symptoms, and determinations may also employ questionnaires that are administered to the patient, such as quality-of-life questionnaires.

Various indicators that reflect the extent of the patient's illness may be assessed for determining whether the amount and time of the treatment is sufficient. The baseline value for the chosen indicator or indicators is established by examination of the patient  
10 prior to administration of the first dose of the etanercept or other TNF $\alpha$  inhibitor. Preferably, the baseline examination is done within about 60 days of administering the first dose. If the TNF $\alpha$  antagonist is being administered to treat acute symptoms, such as for example to treat a traumatic knee injury, the first dose is administered as soon as practically possible after the injury has occurred.

15 Improvement is induced by administering TNFR:Fc or other TNF $\alpha$  antagonist until the patient manifests an improvement over baseline for the chosen indicator or indicators. In treating chronic conditions, this degree of improvement is obtained by repeatedly administering this medicament over a period of at least a month or more, e.g., for one, two, or three months or longer, or indefinitely. A period of one to six weeks, or  
20 even a single dose, often is sufficient for treating acute conditions. For injuries or acute conditions, a single dose may be sufficient.

Although the extent of the patient's illness after treatment may appear improved according to one or more indicators, treatment may be continued indefinitely at the same level or at a reduced dose or frequency. Once treatment has been reduced or  
25 discontinued, it later may be resumed at the original level if symptoms should reappear.

Any efficacious route of administration may be used to therapeutically administer TNFR:Fc or other TNF $\alpha$  antagonists. If injected, TNFR:Fc can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes by bolus injection or by continuous infusion. Other suitable means  
30 of administration include sustained release from implants, aerosol inhalation, eyedrops, oral preparations, including pills, syrups, lozenges or chewing gum, and topical preparations such as lotions, gels, sprays, ointments or other suitable techniques. Alternatively, proteinaceous TNF $\alpha$  inhibitors, such as a soluble TNFR, may be administered by implanting cultured cells that express the protein, for example, by  
35 implanting cells that express TNFR:Fc. In one embodiment, the patient's own cells are induced to produce TNFR:Fc by transfection *in vivo* or *ex vivo* with a DNA that encodes TNFR:Fc. This DNA can be introduced into the patient's cells, for example, by injecting

5 naked DNA or liposome-encapsulated DNA that encodes TNFR:Fc, or by other means of transfection. When TNFR:Fc is administered in combination with one or more other biologically active compounds, these may be administered by the same or by different routes, and may be administered simultaneously, separately or sequentially.

10 TNFR:Fc or other soluble TNFRs preferably are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. Such carriers are nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the TNF $\alpha$  antagonist with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those  
15 having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. In accordance with appropriate industry standards, preservatives may also be added, such as benzyl alcohol. TNFR:Fc preferably is  
20 formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in standard dosing trials, and may vary according to the chosen route of administration. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the age and condition of the patient, and so  
25 forth.

In one embodiment of the invention, TNFR:Fc is administered one time per week to treat the various medical disorders disclosed herein, in another embodiment is administered at least two times per week, and in another embodiment is administered at least three times per week. An adult patient is a person who is 18 years of age or older.  
30 If injected, the effective amount of TNFR:Fc per adult dose ranges from 1-20 mg/m<sup>2</sup>, and preferably is about 5-12 mg/m<sup>2</sup>. Alternatively, a flat dose may be administered, whose amount may range from 5-100 mg/dose. Exemplary dose ranges for a flat dose to be administered by subcutaneous injection are 5-25 mg/dose, 25-50 mg/dose and 50-100 mg/dose. In one embodiment of the invention, the various indications described  
35 below are treated by administering a preparation acceptable for injection containing TNFR:Fc at 25 mg/dose, or alternatively, containing 50 mg per dose. The 25 mg or 50 mg dose may be administered repeatedly, particularly for chronic conditions. If a



5 route of administration other than injection is used, the dose is appropriately adjusted in  
accord with standard medical practices. In many instances, an improvement in a patient's  
condition will be obtained by injecting a dose of about 25 mg of TNFR:Fc one to three  
times per week over a period of at least three weeks, or a dose of 50 mg of TNFR:Fc one  
or two times per week for at least three weeks, though treatment for longer periods may  
10 be necessary to induce the desired degree of improvement. For incurable chronic  
conditions, the regimen may be continued indefinitely, with adjustments being made to  
dose and frequency if such are deemed necessary by the patient's physician.

For pediatric patients (age 4-17), a suitable regimen involves the subcutaneous  
injection of 0.4 mg/kg, up to a maximum dose of 25 mg of TNFR:Fc, administered by  
15 subcutaneous injection one or more times per week.

The invention further includes the administration of TNFR:Fc concurrently with  
one or more other drugs that are administered to the same patient in combination with the  
TNFR:Fc, each drug being administered according to a regimen suitable for that  
medicament. "Concurrent administration" encompasses simultaneous or sequential  
20 treatment with the components of the combination, as well as regimens in which the  
drugs are alternated, or wherein one component is administered long-term and the  
other(s) are administered intermittently. Components may be administered in the same or  
in separate compositions, and by the same or different routes of administration.  
Examples of drugs to be administered concurrently include but are not limited to  
25 antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines,  
DMARDs and non-steroidal anti-inflammatories. DMARDs that can be administered in  
combination with the subject TNF $\alpha$  inhibitors such as TNFR:Fc include azathioprine,  
cyclophosphamide, cyclosporine, hydroxychloroquine sulfate, methotrexate, leflunomide,  
minocycline, penicillamine, sulfasalazine and gold compounds such as oral gold, gold  
30 sodium thiomalate and aurothioglucose. Additionally, TNFR:Fc may be combined with a  
second TNF $\alpha$  antagonist, including an antibody against TNF $\alpha$  or TNFR, a TNF $\alpha$ -derived  
peptide that acts as a competitive inhibitor of TNF $\alpha$  (such as those described in  
U.S. 5,795,859), a TNFR-IgG fusion protein other than etanercept, such as one containing  
the extracellular portion of the p55 TNF $\alpha$  receptor, a soluble TNFR other than an IgG  
35 fusion protein, or other molecules that reduce endogenous TNF $\alpha$  levels, such as inhibitors  
of the TNF $\alpha$  converting enzyme (see e.g., U.S. 5,594,106). In further embodiments of

5 this invention, TNFR:Fc is administered in combination with pentoxifylline or thalidomide.

If an antibody against TNF $\alpha$  is used as the TNF $\alpha$  inhibitor, a preferred dose range is 0.1 to 20 mg/kg, and more preferably is 1-10 mg/kg. Another preferred dose range for anti-TNF $\alpha$  antibody is 0.75 to 7.5 mg/kg of body weight. Humanized antibodies are  
10 preferred, that is, antibodies in which only the antigen-binding portion of the antibody molecule is derived from a non-human source. such antibodies may be injected or administered intravenously.

In one preferred embodiment of the invention, the various medical disorders disclosed herein as being treatable with inhibitors such as TNFR:Fc are treated in  
15 combination with another cytokine or cytokine inhibitor. For example, TNFR:Fc may be administered in a composition that also contains a compound that inhibits the interaction of other inflammatory cytokines with their receptors. Examples of cytokine inhibitors used in combination with TNFR:Fc include, for example, antagonists of TGF $\beta$ , Il-6 or Il-8. TNF $\alpha$  inhibitors such as TNFR:Fc also may be administered in combination with  
20 the cytokines GM-CSF, IL-2 and inhibitors of protein kinase A type 1 to enhance T cell proliferation in HIV-infected patients who are receiving anti-retroviral therapy. Other combinations for treating the hereindescribed diseases include TNFR:Fc administered concurrently with compounds that block the binding of RANK and RANK-ligand, such as antagonistic antibodies against RANK or RANK-ligand, soluble forms of RANK-ligand that do not trigger RANK, osteoprotegerin or soluble forms of RANK, including  
25 RANK:Fc. Soluble forms of RANK suitable for these combinations are described, for example, in U.S. 6,017,729. The concurrent administration of TNFR:Fc and RANK:Fc or TNFR:Fc and osteoprotegerin is useful for preventing bone destruction in various settings including but not limited to various rheumatic disorders, osteoporosis, multiple myeloma or other malignancies that cause bone degeneration, or anti-tumor therapy aimed at  
30 preventing metastasis to bone, or bone destruction associated with prosthesis wear debris or with periodontitis.

The present invention also relates to the use of the disclosed TNF $\alpha$  inhibitors, such as TNFR:Fc, in the manufacture of a medicament for the prevention or therapeutic  
35 treatment of each medical disorder disclosed herein.

The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies described herein are useful in medicines for treating bacterial, viral or protozoal infections, and

5 complications resulting therefrom. One such disease is *Mycoplasma pneumonia*. In  
 addition, provided herein is the use of TNFR:Fc to treat AIDS and related conditions,  
 such as AIDS dementia complex, AIDS associated wasting, lipodystrophy due to  
 antiretroviral therapy; and Kaposi's sarcoma. Provided herein is the use of TNFR:Fc for  
 treating protozoal diseases, including malaria and schistosomiasis. Additionally provided  
 10 is the use of TNFR:Fc to treat erythema nodosum leprosum; bacterial or viral meningitis;  
 tuberculosis, including pulmonary tuberculosis; and pneumonitis secondary to a bacterial  
 or viral infection. Provided also herein is the use of TNFR:Fc to prepare medicaments for  
 treating louse-borne relapsing fevers, such as that caused by *Borrelia recurrentis*.  
 TNFR:Fc can also be used to prepare a medicament for treating conditions caused by  
 15 *Herpes* viruses, such as herpetic stromal keratitis, corneal lesions, and virus-induced  
 corneal disorders. In addition, TNFR:Fc can be used in treating human papillomavirus  
 infections. TNFR:Fc is used also to prepare medicaments to treat influenza.

Cardiovascular disorders are treatable with the disclosed TNF $\alpha$  inhibitors,  
 pharmaceutical compositions or combination therapies, including aortic aneurisms;  
 20 arteritis; vascular occlusion, including cerebral artery occlusion; complications of  
 coronary by-pass surgery; ischemia/reperfusion injury; heart disease, including  
 atherosclerotic heart disease, myocarditis, including chronic autoimmune myocarditis and  
 viral myocarditis; heart failure, including chronic heart failure (CHF), cachexia of heart  
 failure; myocardial infarction; restenosis after heart surgery; silent myocardial ischemia;  
 25 post-implantation complications of left ventricular assist devices; Raynaud's phenomena;  
 thrombophlebitis; vasculitis, including Kawasaki's vasculitis; giant cell arteritis,  
 Wegener's granulomatosis; and Schoenlein-Henoch purpura.

TNF $\alpha$  and IL-8 have been implicated as chemotactic factors in atherosclerotic  
 abdominal aortic aneurism (Szekanecz et al., *Pathobiol* 62:134-139 (1994)). Abdominal  
 30 aortic aneurism may be treated in human patients by administering a soluble TNFR, such  
 as TNFR:Fc, which may be administered in combination with an inhibitor of IL-8, such  
 treatment having the effect of reducing the pathological neovascularization associated  
 with this condition.

A combination of a TNF $\alpha$  inhibitor and one or more other anti-angiogenesis  
 35 factors may be used to treat solid tumors, thereby reducing the vascularization that  
 nourishes the tumor tissue. Suitable anti-angiogenic factors for such combination  
 therapies include IL-8 inhibitors, angiostatin, endostatin, krigle 5, inhibitors of vascular

5     endothelial growth factor (such as antibodies against vascular endothelial growth factor),  
angiopoietin-2 or other antagonists of angiopoietin-1, antagonists of platelet-activating  
factor and antagonists of basic fibroblast growth factor

10     In addition, the subject TNF $\alpha$  inhibitors, compositions and combination therapies  
are used to treat chronic pain conditions, such as chronic pelvic pain, including chronic  
prostatitis/pelvic pain syndrome. As a further example, TNFR:Fc and the compositions  
and combination therapies of the invention are used to treat post-herpetic pain.

15     Provided also are methods for using TNF $\alpha$  inhibitors, compositions or  
combination therapies to treat various disorders of the endocrine system. For example,  
the TNF $\alpha$  inhibitors are used to treat juvenile onset diabetes (includes autoimmune and  
insulin-dependent types of diabetes) and also to treat maturity onset diabetes (includes  
non-insulin dependent and obesity-mediated diabetes). In addition, the subject  
compounds, compositions and combination therapies are used to treat secondary  
conditions associated with diabetes, such as diabetic retinopathy, kidney transplant  
rejection in diabetic patients, obesity-mediated insulin resistance, and renal failure, which  
20     itself may be associated with proteinuria and hypertension. Other endocrine disorders  
also are treatable with these compounds, compositions or combination therapies,  
including polycystic ovarian disease, X-linked adrenoleukodystrophy, hypothyroidism  
and thyroiditis, including Hashimoto's thyroiditis (i.e., autoimmune thyroiditis).

25     Conditions of the gastrointestinal system also are treatable with TNF $\alpha$  inhibitors,  
compositions or combination therapies, including coeliac disease. In addition, the  
compounds, compositions and combination therapies of the invention are used to treat  
Crohn's disease; ulcerative colitis; idiopathic gastroparesis; pancreatitis, including  
chronic pancreatitis and lung injury associated with acute pancreatitis; and ulcers,  
including gastric and duodenal ulcers.

30     Included also are methods for using the subject TNF $\alpha$  inhibitors, compositions or  
combination therapies for treating disorders of the genitourinary system, such as  
glomerulonephritis, including autoimmune glomerulonephritis, glomerulonephritis due to  
exposure to toxins or glomerulonephritis secondary to infections with haemolytic  
streptococci or other infectious agents. Also treatable with the compounds, compositions  
35     and combination therapies of the invention are uremic syndrome and its clinical  
complications (for example, renal failure, anemia, and hypertrophic cardiomyopathy),  
including uremic syndrome associated with exposure to environmental toxins, drugs or

5 other causes. Further conditions treatable with the compounds, compositions and combination therapies of the invention are complications of hemodialysis; prostate conditions, including benign prostatic hypertrophy, nonbacterial prostatitis and chronic prostatitis; and complications of hemodialysis.

Also provided herein are methods for using TNF $\alpha$  inhibitors, compositions or  
10 combination therapies to treat various hematologic and oncologic disorders. For example, TNFR:Fc is used to treat various forms of cancer, including acute myelogenous leukemia, Epstein-Barr virus-positive nasopharyngeal carcinoma, glioma, colon, stomach, prostate, renal cell, cervical and ovarian cancers, lung cancer (SCLC and NSCLC), including cancer-associated cachexia, fatigue, asthenia, paraneoplastic syndrome of  
15 cachexia and hypercalcemia. Additional diseases treatable with the subject TNF $\alpha$  inhibitors, compositions or combination therapies are solid tumors, including sarcoma, osteosarcoma, and carcinoma, such as adenocarcinoma (for example, breast cancer) and squamous cell carcinoma. In addition, the subject compounds, compositions or combination therapies are useful for treating leukemia, including acute myelogenous  
20 leukemia, chronic or acute lymphoblastic leukemia and hairy cell leukemia. Other malignancies with invasive metastatic potential can be treated with the subject compounds, compositions and combination therapies, including multiple myeloma. In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies can be used to treat anemias and hematologic disorders, including anemia of chronic disease,  
25 aplastic anemia, including Fanconi's aplastic anemia; idiopathic thrombocytopenic purpura (ITP); myelodysplastic syndromes (including refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation); myelofibrosis/myeloid metaplasia; and sickle cell vasocclusive crisis.

30 Various lymphoproliferative disorders also are treatable with the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies. These include, but are not limited to autoimmune lymphoproliferative syndrome (ALPS), chronic lymphoblastic leukemia, hairy cell leukemia, chronic lymphatic leukemia, peripheral T-cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt's  
35 lymphoma, Epstein-Barr virus-positive T cell lymphoma, histiocytic lymphoma, Hodgkin's disease, diffuse aggressive lymphoma, acute lymphatic leukemias, T gamma

- 5 lymphoproliferative disease, cutaneous B cell lymphoma, cutaneous T cell lymphoma (i.e., mycosis fungoides) and Sézary syndrome.

In addition, the subject TNF $\alpha$  inhibitors, compositions and combination therapies are used to treat hereditary conditions such as Gaucher's disease, Huntington's disease, linear IgA disease, and muscular dystrophy.

- 10 Other conditions treatable by the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies include those resulting from injuries to the head or spinal cord, and including subdural hematoma due to trauma to the head.

- The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are further used to treat conditions of the liver such as hepatitis, including acute alcoholic  
15 hepatitis, acute drug-induced or viral hepatitis, hepatitis A, B and C, sclerosing cholangitis and inflammation of the liver due to unknown causes.

- In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are used to treat various disorders that involve hearing loss and that are associated with abnormal TNF $\alpha$  expression. One of these is inner ear or cochlear nerve-  
20 associated hearing loss that is thought to result from an autoimmune process, i.e., autoimmune hearing loss. This condition currently is treated with steroids, methotrexate and/or cyclophosphamide, which may be administered concurrently with the TNFR:Fc or other TNF $\alpha$  inhibitor. Also treatable with the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies is cholesteatoma, a middle ear disorder often associated with  
25 hearing loss.

- In addition, the subject invention provides TNF $\alpha$  inhibitors, compositions and combination therapies for the treatment of non-arthritis medical conditions of the bones and joints. This encompasses osteoclast disorders that lead to bone loss, such as but not limited to osteoporosis, including post-menopausal osteoporosis, periodontitis resulting in  
30 tooth loosening or loss, and prosthesis loosening after joint replacement (generally associated with an inflammatory response to wear debris). This latter condition also is called "orthopedic implant osteolysis." Another condition treatable by administering TNFR $\alpha$  inhibitors, such as TNFR:Fc, is temporal mandibular joint dysfunction (TMJ).

- A number of pulmonary disorders also can be treated with the disclosed TNF $\alpha$   
35 inhibitors, compositions and combination therapies. One such condition is adult respiratory distress syndrome (ARDS), which is associated with elevated TNF $\alpha$ , and may be triggered by a variety of causes, including exposure to toxic chemicals, pancreatitis,

5 trauma or other causes. The disclosed compounds, compositions and combination  
therapies of the invention also are useful for treating broncho-pulmonary dysplasia  
(BPD); lymphangioleiomyomatosis; and chronic fibrotic lung disease of preterm infants.  
In addition, the compounds, compositions and combination therapies of the invention are  
used to treat occupational lung diseases, including asbestosis, coal worker's  
10 pneumoconiosis, silicosis or similar conditions associated with long-term exposure to fine  
particles. In other aspects of the invention, the disclosed compounds, compositions and  
combination therapies are used to treat pulmonary disorders, including chronic  
obstructive pulmonary disease (COPD) associated with chronic bronchitis or emphysema;  
fibrotic lung diseases, such as cystic fibrosis, idiopathic pulmonary fibrosis and radiation-  
15 induced pulmonary fibrosis; pulmonary sarcoidosis; and allergies, including allergic  
rhinitis, contact dermatitis, atopic dermatitis and asthma.

Cystic fibrosis is an inherited condition characterized primarily by the  
accumulation of thick mucus, predisposing the patient to chronic lung infections and  
obstruction of the pancreas, which results in malabsorption of nutrients and malnutrition.  
20 TNFR:Fc may be administered to treat cystic fibrosis. If desired, treatment with  
TNFR:Fc may be administered concurrently with corticosteroids, mucus-thinning agents  
such as inhaled recombinant deoxyribonuclease I (such as PULMOZYME®; Genentech,  
Inc.) or inhaled tobramycin (TOBI®; Pathogenesis, Inc.). TNFR:Fc also may be  
administered concurrently with corrective gene therapy, drugs that stimulate cystic  
25 fibrosis cells to secrete chloride or other yet-to-be-discovered treatments. Sufficiency of  
treatment may be assessed, for example, by observing a decrease in the number of  
pathogenic organisms in sputum or lung lavage (such as *Haemophilus influenzae*,  
*Staphylococcus aureus*, and *Pseudomonas aeruginosa*), by monitoring the patient for  
weight gain, by detecting an increase in lung capacity or by any other convenient means.

30 TNFR:Fc or TNFR:Fc combined with the cytokine IFN $\gamma$ -1b (such as  
ACTIMMUNE®; InterMune Pharmaceuticals) may be used for treating cystic fibrosis or  
fibrotic lung diseases, such as idiopathic pulmonary fibrosis, radiation-induced  
pulmonary fibrosis and bleomycin-induced pulmonary fibrosis. In addition, this  
combination is useful for treating other diseases characterized by organ fibrosis, including  
35 systemic sclerosis (also called "scleroderma"), which often involves fibrosis of the liver.  
For treating cystic fibrosis, TNFR:Fc and IFN $\gamma$ -1b may be combined with  
PULMOZYME® or TOBI® or other treatments for cystic fibrosis.

5 TNFR:Fc alone or in combination with IFN $\gamma$ -1b may be administered together with other treatments presently used for treating fibrotic lung disease. Such additional treatments include glucocorticoids, azathioprine, cyclophosphamide, penicillamine, colchicine, supplemental oxygen and so forth. Patients with fibrotic lung disease, such as IPF, often present with nonproductive cough, progressive dyspnea, and show a  
10 restrictive ventilatory pattern in pulmonary function tests. Chest radiographs reveal fibrotic accumulations in the patient's lungs. When treating fibrotic lung disease in accord with the disclosed methods, sufficiency of treatment may be detected by observing a decrease in the patient's coughing (when cough is present), or by using standard lung function tests to detect improvements in total lung capacity, vital capacity, residual lung  
15 volume or by administering a arterial blood gas determination measuring desaturation under exercising conditions, and showing that the patient's lung function has improved according to one or more of these measures. In addition, patient improvement may be determined through chest radiography results showing that the progression of fibrosis in the patient's lungs has become arrested or reduced.

20 In addition, TNF inhibitors (including soluble TNFRs or antibodies against TNF $\alpha$  or TNFR) are useful for treating organ fibrosis when administered in combination with relaxin, a hormone that down-regulates collagen production thus inhibiting fibrosis, or when given in combination with agents that block the fibrogenic activity of TGF- $\beta$ . Combination therapies using TNFR:Fc and recombinant human relaxin are useful, for  
25 example, for treating systemic sclerosis or fibrotic lung diseases, including cystic fibrosis, idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis and bleomycin-induced pulmonary fibrosis.

Other embodiments provide methods for using the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies to treat a variety of rheumatic disorders. These  
30 include: adult and juvenile rheumatoid arthritis; systemic lupus erythematosus; gout; osteoarthritis; polymyalgia rheumatica; seronegative spondylarthropathies, including ankylosing spondylitis; and Reiter's disease. The subject TNF $\alpha$  inhibitors, compositions and combination therapies are used also to treat psoriatic arthritis and chronic Lyme arthritis. Also treatable with these compounds, compositions and combination therapies  
35 are Still's disease and uveitis associated with rheumatoid arthritis. In addition, the compounds, compositions and combination therapies of the invention are used in treating disorders resulting in inflammation of the voluntary muscle, including dermatomyositis



5 and polymyositis. Moreover, the compounds, compositions and combinations disclosed herein are useful for treating sporadic inclusion body myositis, as TNF $\alpha$  may play a significant role in the progression of this muscle disease. In addition, the compounds, compositions and combinations disclosed herein are used to treat multicentric reticulohistiocytosis, a disease in which joint destruction and papular nodules of the face  
10 and hands are associated with excess production of proinflammatory cytokines by multinucleated giant cells.

For purposes of this invention, patients are defined as having psoriatic arthritis (PsA) if they have one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails. The psoriatic lesions may  
15 appear before or after the onset of swollen or tender joints. It is understood that prior to treatment, manifestations of PsA may have persisted over time, e.g., for several months or years, and may involve several joints. According to one classification system (reviewed in Alonso et al., 1991), PsA patients can be categorized based on their arthritic symptoms into five clinical subgroups: 1) DIP; 2) mutilans arthritis; 3) symmetrical polyarthritis;  
20 4) oligoarticular arthritis; and 5) ankylosing spondylitis-like. The disclosed therapies, compounds and compositions are suitable for treating all five forms of PsA.

The TNF $\alpha$  inhibitors, compositions and combination therapies of the invention may be used to inhibit hypertrophic scarring, a phenomenon believed to result in part from excessive TNF $\alpha$  secretion. TNF inhibitors may be administered alone or  
25 concurrently with other agents that inhibit hypertrophic scarring, such as inhibitors of TGF- $\alpha$ .

Cervicogenic headache is a common form of headache arising from dysfunction in the neck area, and which is associated with elevated levels of TNF $\alpha$ , which are believed to mediate an inflammatory condition that contributes to the patient's discomfort  
30 (Martelletti, *Clin Exp Rheumatol* 18(2 Suppl 19):S33-8 (Mar-Apr, 2000)). Cervicogenic headache may be treated by administering an inhibitor of TNF $\alpha$  as disclosed herein, thereby reducing the inflammatory response and associated headache pain.

The TNF $\alpha$  inhibitors, compositions and combination therapies of the invention are useful for treating primary amyloidosis. In addition, the secondary amyloidosis that is  
35 characteristic of various conditions also are treatable with TNF $\alpha$  inhibitors such as TNFR:Fc, and the compositions and combination therapies described herein. Such conditions include: Alzheimer's disease, secondary reactive amyloidosis; Down's

5 syndrome; and dialysis-associated amyloidosis. Also treatable with the compounds, compositions and combination therapies of the invention are inherited periodic fever syndromes, including familial Mediterranean fever, hyperimmunoglobulin D and periodic fever syndrome and TNF-receptor associated periodic syndromes (TRAPS).

10 Disorders associated with transplantation also are treatable with the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies, such as graft-versus-host disease, and complications resulting from solid organ transplantation, including transplantation of heart, liver, lung, skin, kidney or other organs. TNFR:Fc may be administered, for example, to prevent or inhibit the development of bronchiolitis obliterans after lung transplantation. Patients undergoing autologous hematopoietic stem  
15 cell transplantation in the form of peripheral blood stem cell transplantation may develop "engraftment syndrome," or "ES," which is an adverse and generally self-limited response that occurs about the time of hematopoietic engraftment and which can result in pulmonary deterioration. ES may be treated with inhibitors of either IL-8 or TNF $\alpha$  (such as TNFR:Fc), or with a combination of inhibitors against both of these cytokines.

20 Ocular disorders also are treatable with the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies, including rhegmatogenous retinal detachment, and inflammatory eye disease, and inflammatory eye disease associated with smoking and macular degeneration.

25 TNF $\alpha$  inhibitors such as TNFR:Fc and the disclosed compositions and combination therapies also are useful for treating disorders that affect the female reproductive system. Examples include, but are not limited to, multiple implant failure/infertility; fetal loss syndrome or IV embryo loss (spontaneous abortion); preeclamptic pregnancies or eclampsia; and endometriosis.

30 In addition, the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies are useful for treating obesity, including treatment to bring about a decrease in leptin formation. Also, the compounds, compositions and combination therapies of the invention are used to treat sciatica, symptoms of aging, severe drug reactions (for example, Il-2 toxicity or bleomycin-induced pneumopathy and fibrosis), or to suppress the inflammatory response prior, during or after the transfusion of allogeneic red blood  
35 cells in cardiac or other surgery, or in treating a traumatic injury to a limb or joint, such as traumatic knee injury. Various other medical disorders treatable with the disclosed TNF $\alpha$  inhibitors, compositions and combination therapies include; multiple sclerosis; Behcet's

5 syndrome; Sjogren's syndrome; autoimmune hemolytic anemia; beta thalassemia; amyotrophic lateral sclerosis (Lou Gehrig's Disease); Parkinson's disease; and tenosynovitis of unknown cause, as well as various autoimmune disorders or diseases associated with hereditary deficiencies.

10 The disclosed TNF $\alpha$  inhibitors, compositions and combination therapies furthermore are useful for treating acute polyneuropathy; anorexia nervosa; Bell's palsy; chronic fatigue syndrome; transmissible dementia, including Creutzfeld-Jacob disease; demyelinating neuropathy; Guillain-Barre syndrome; vertebral disc disease; Gulf war syndrome; myasthenia gravis; silent cerebral ischemia; sleep disorders, including narcolepsy and sleep apnea; chronic neuronal degeneration; and stroke, including cerebral  
15 ischemic diseases.

Disorders involving the skin or mucous membranes also are treatable using the disclosed TNF $\alpha$  inhibitors, compositions or combination therapies. Such disorders include acantholytic diseases, including Darier's disease, keratosis follicularis and pemphigus vulgaris. Also treatable with the subject TNF $\alpha$  inhibitors, compositions and  
20 combination therapies are acne; acne rosacea; alopecia areata; aphthous stomatitis; bullous pemphigoid; burns; eczema; erythema, including erythema multiforme and erythema multiforme bullosum (Stevens-Johnson syndrome); inflammatory skin disease; lichen planus; linear IgA bullous disease (chronic bullous dermatosis of childhood); loss of skin elasticity; mucosal surface ulcers; neutrophilic dermatitis (Sweet's syndrome);  
25 pityriasis rubra pilaris; psoriasis; pyoderma gangrenosum; and toxic epidermal necrolysis.

Patients are defined as having ordinary psoriasis if they lack the more serious symptoms of PsA (e.g., distal interphalangeal joint DIP involvement, enthesopathy, spondylitis and dactylitis) but have one of the following: 1) inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris); 2) small red dots  
30 appearing on the trunk, arms or legs (guttate psoriasis); 3) smooth inflamed lesions without scaling in the flexural surfaces of the skin (inverse psoriasis); 4) widespread reddening and exfoliation of fine scales, with or without itching and swelling (erythrodermic psoriasis); 5) blister-like lesions (pustular psoriasis); 6) elevated inflamed scalp lesions covered by silvery white scales (scalp psoriasis); 7) pitted fingernails, with  
35 or without yellowish discoloration, crumbling nails, or inflammation and detachment of the nail from the nail bed (nail psoriasis).

5 Ordinary psoriasis may be treated by administering to a human patient compositions containing a therapeutically effective amount of a TNF $\alpha$  inhibitor such as a soluble TNF receptor or an antibody against TNF $\alpha$ .

10 In one preferred embodiment, the therapeutic agent is a soluble TNF receptor, and preferably is a TNFR-Ig. In a preferred embodiment, the TNFR-Ig is TNFR:Fc, which may be administered in the form of a pharmaceutically acceptable composition as described herein. Psoriasis may be treated by administering TNFR:Fc one or more times per week by subcutaneous injection, although other routes of administration may be used if desired. In one exemplary regimen for treating adult human patients, 25 mg of TNFR:Fc is administered by subcutaneous injection two times per week or three times  
15 per week for one or more weeks, and preferably for four or more weeks. Alternatively, a dose of 5-12 mg/m<sup>2</sup> or a flat dose of 50 mg is injected subcutaneously one time or two times per week for one or more weeks. In other embodiments, psoriasis is treated with TNFR:Fc in a sustained-release form, such as TNFR:Fc that is encapsulated in a biocompatible polymer, TNFR:Fc that is admixed with a biocompatible polymer (such as  
20 topically applied hydrogels), and TNFR:Fc that is encased in a semi-permeable implant.

Various other medicaments used to treat ordinary psoriasis may also be administered concurrently with compositions comprising TNF $\alpha$  inhibitors, such as TNFR:Fc. Such medicaments include: NSAIDs; DMARDs; analgesics; topical steroids; systemic steroids (e.g., prednisone); cytokines; antagonists of inflammatory cytokines;  
25 antibodies against T cell surface proteins; anthralin; coal tar; vitamin D3 and its analogs; topical retinoids; oral retinoids; salicylic acid; and hydroxyurea. Suitable analgesics for such combinations include: acetaminophen, codeine, propoxyphene napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol. DMARDs suitable for such combinations include: azathioprine, cyclophosphamide, cyclosporine,  
30 hydroxychloroquine sulfate, methotrexate, leflunomide, minocycline, penicillamine, sulfasalazine, oral gold, gold sodium thiomalate and aurothioglucose. In addition, the TNFR:Fc or other TNFR mimic may be administered in combination with antimalarials or colchicine. NSAIDs suitable for the subject combination treatments of psoriasis include: salicylic acid (aspirin) and salicylate derivatives; ibuprofen; indomethacin;  
35 celecoxib; rofecoxib; ketorolac; nambumetone; piroxicam; naproxen; oxaprozin; sulindac; ketoprofen; diclofenac; and other COX-1 and COX-2 inhibitors, propionic acid derivatives, acetic acid derivatives, fumaric acid derivatives, carboxylic acid derivatives,

5 butyric acid derivatives, oxicams, pyrazoles and pyrazolones, including newly developed anti-inflammatories.

If an antagonist against an inflammatory cytokine is administered concurrently with TNFR:Fc to treat psoriasis, suitable targets for such antagonists include TGF $\beta$ , Il-6 and Il-8.

10 In addition, TNFR:Fc may be used to treat psoriasis in combination with topical steroids, systemic steroids, antagonists of inflammatory cytokines, antibodies against T cell surface proteins, anthralin, coal tar, vitamin D3 and its analogs (including 1,25-dihydroxy vitamin D3 and calcipotriene), topical retinoids, oral retinoids (including but not limited to etretinate, acitretin and isotretinoin), topical salicylic acid,  
15 methotrexate, cyclosporine, hydroxyurea and sulfasalazine. In addition, TNFR:Fc may be administered to treat psoriasis in combination with one or more of the following compounds; minocycline; misoprostol; oral collagen; 6-mercaptopurine; nitrogen mustard; gabapentin; bromocriptine; somatostatin; peptide T; anti-CD4 monoclonal antibody; fumaric acid; polyunsaturated ethyl ester lipids; zinc; and other drugs that may  
20 be used to treat psoriasis. TNFR:Fc may also be used to treat psoriasis in combination with the use of various oils, including fish oils, nut oils and vegetable oils; aloe vera; jojoba; Dead Sea salts; capsaicin; milk thistle; witch hazel; moisturizers; and Epsom salts. In addition, psoriasis may be treated with compositions containing TNFR:Fc in combination with the following therapies: plasmapheresis; phototherapy with ultraviolet  
25 light B; psoralen combined with ultraviolet light A (PUVA); and sunbathing.

For determining the sufficiency of treatment when treating ordinary psoriasis in accord with the invention, the TNFR:Fc (or other TNF $\alpha$  inhibitor) is administered in an amount and for a time sufficient to induce an improvement in an indicator such as psoriasis area and severity index (PASI) or an improvement in Target Lesion Assessment  
30 score, which is an index for assessing the severity of individual skin lesions. In one embodiment, the treatment is regarded as sufficient when the patient exhibits an at least 50% improvement in his or her PASI score, and in another embodiment, when the patient exhibits an at least 75% improvement in PASI score. The sufficiency of treatment for psoriasis may also be determined by evaluating individual psoriatic lesions for  
35 improvement in severity (Psoriasis Target Lesion Assessment Score), and continuing treatment until an improvement is noted according to this scoring system. This scoring system involves determining for an individual lesion whether improvement has occurred

5 in plaque elevation, amount and degree of scaling or degree of erythema, and target lesion response to treatment, each of which is separately scored. Psoriasis Target Lesion Assessment Score is determined by adding together the separate scores for all four of the aforementioned indicia.

10 In addition to human patients, inhibitors of TNF $\alpha$  are useful in the treatment of autoimmune and inflammatory conditions in non-human animals, such as pets (dogs, cats, birds, primates, etc.), domestic farm animals (horses cattle, sheep, pigs, birds, etc.), or any animal that suffers from a TNF $\alpha$ -mediated inflammatory or arthritic condition. In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the dose is determined  
15 according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m<sup>2</sup>, or more preferably, from 5-12 mg/m<sup>2</sup>. For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. In a preferred embodiment, TNFR:Fc (preferably constructed from genes derived from the same species as the patient), or another soluble TNFR mimic, is administered by injection or other suitable route one or more times per week until the  
20 animal's condition is improved, or it may be administered indefinitely.

### EXAMPLE

#### Evaluation of TNFR:Fc in Patients with Psoriatic Arthritis.

Sixty patients with active psoriatic arthritis (PsA) were enrolled in a Phase II double-blind, randomized, placebo controlled study to determine whether the  
25 subcutaneous biweekly administration of etanercept (recombinant TNFR:Fc) was safe in this patient population and whether efficacy could be documented for both the arthritic and psoriatic aspects of this disease.

In this study, a flat dose of 25 mg of TNFR:Fc was injected subcutaneously two times a week. After 12 weeks, patients who completed the study were eligible for  
30 continuation into a 24 week open-label extension of the study, with assessments made at weeks 16, 36 and 30 days post-study. All patients participating in the study extension received etanercept, including those patients who had received placebo during the blinded portion of the study.

In order to qualify for enrollment, subjects had to have at least one of the  
35 following forms of PsA: 1) DIP involvement; 2) polyarticular arthritis, absence of rheumatoid nodules and presence of psoriasis; 3) arthritis mutilans; 4) asymmetric peripheral arthritis; or 5) ankylosing spondylitis-like PsA. Subjects furthermore had to

5 exhibit three or more swollen joints and three or more tender or painful joints at the time  
of enrollment, and to have exhibited an inadequate response to NSAID therapy. Subjects  
who were on other medications, including methotrexate, NSAIDs or oral corticosteroids  
were permitted to continue these other treatments at the same dose so long as the  
investigator considered these other treatments to inadequately control the patient's  
10 disease. Methotrexate was concurrently taken by 47% of the etanercept group, and 47%  
of the placebo group, NSAIDs were concurrently taken by 67% of the etanercept and  
77% of the placebos and oral corticosteroids by 40% of the etanercept and 20% of the  
placebo patients. Pain medications, including acetaminophen, codeine, propoxyphene  
napsylate, oxycodone hydrochloride, hydrocodone bitartrate and tramadol, also were  
15 permitted during the study, as well as the use of topical tar compounds.

To qualify as having PsA, patients had to have experienced at least one psoriatic  
lesion of the skin or nails. Patients were evaluated at baseline (day 1 of treatment) as  
follows: 1) complete joint assessment; 2) psoriasis assessment; 3) duration of morning  
stiffness; 4) health assessment (quality of life) questionnaire, visual analog scale  
20 (HAQ/VAS); 5) patient global assessment; 6) erythrocyte sedimentation rate (ESR,  
Westergren); 7) C-reactive protein (CRP); and 8) urinalysis. At weeks 4 and 8,  
patients were evaluated as follows: 1) complete joint assessment; 2) psoriasis  
assessment; 3) duration of morning stiffness; 4) HAQ/VAS; 5) patient global  
assessment. At the end of 12 weeks, subjects were evaluated as follows:  
25 1) complete joint assessment; 2) psoriasis assessment; 3) focused physical exam;  
4) duration of morning stiffness; 5) HAQ/VAS; 6) patient global assessment;  
6) hematology profile; 7) chemistry profile; 8) ESR; 9) CRP; 10) urinalysis;  
11) serum tested for antibody to TNFR:Fc. Only those patients whose psoriasis  
was stable and covered  $\geq 3\%$  of body area were evaluated for psoriasis response  
30 during this trial, although patients whose psoriasis was inactive or covered less  
area were permitted to enroll.

A primary endpoint for clinical improvement or worsening of PsA was the  
Psoriatic Arthritis Response score, which is a composite score based on the  
following four measures: 1) patient self-assessment; 2) physician assessment; 3)  
35 joint pain or tenderness; 4) joint swelling. Both self- and physician assessments,  
i.e., overall assessment of disease status, were measured according to a five point

5 Likert scale, in which a patient was considered as "improved" if his or her score decreased by one category, or as "worse" if his or her score increased by one category. Joint pain or tenderness was measured on a 5-point scale, wherein 1 = none and 5 = severe (withdrawal on examination). Joint swelling was evaluated on a 4-point scale in which 1 = none; 2 = mild (detectable synovial thickening without loss of bony contour); 3 = moderate (loss of distinctness of bony contours); and 4 = severe (bulging synovial proliferation with cystic characteristics). For this last measure, a decrease in swelling of  $\geq 30\%$  was scored as an "improvement," and an increase in swelling of  $\geq 30\%$  was scored as a "worsening." Patients were classified as "improved" under the Psoriatic Arthritis Response scoring system if they exhibited an improvement in at least two of the four measures described above, provided that one of the improved areas was joint pain or joint tenderness, and where there was no worsening in any of the four measures.

In addition, a secondary endpoint used for assessing psoriatic arthritis was a modified version of the American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis (modified ACR 20 response) (Felson et al., 1995). To qualify as "improved" according to this measure, a patient must have exhibited  $\geq 20\%$  improvement in both tender joint count (78 joints assessed) and swollen joint count (76 joints assessed), and also must have shown an improvement in three of the following five: 1) subject pain assessment; 2) subject global assessment; 3) physician global assessment; 4) subject self-assessed disability; 5) acute-phase reactant (Westergreen erythrocyte sedimentation rate or C-reactive protein level). The joint count was done by scoring several different aspects of tenderness, such as pressure and joint manipulation on physical examination, wherein each joint was scored as "tender" or "nontender." Similarly, each joint is scored after physical examination as "swollen" or "not swollen." The subject's pain assessment was based on a horizontal visual analog scale (usually 10 cm) or Likert scale. The subject's and physician's global assessments of the subject's current disease status was based on an anchored horizontal visual analog scale (usually 10 cm), or Likert scale response. The subject's self-assessment of disability was based on any of the following measures, all of which have been validated in RA trials: Arthritis Impact Measurement Scale (AIMS); Health Assessment



- 5 Questionnaire ; the Quality (or Index) of Well Being Scale; the McMaster Health Inventory Questionnaire (MHIQ); and the McMaster-Toronto Arthritis patient preference questionnaire (MACTAR).

A primary endpoint used to assess the psoriatic aspects of PsA was the standard psoriasis area and severity index (PASI) (Fredriksson and Petersson, *Dermatologica* 10 157:238-244, 1978). For this study, a positive treatment response was defined as an at least 50% or an at least 75% improvement in a patient's PASI score. For assessing area and severity, the body is divided into four regions: head (10%); trunk (30%); upper extremities (20%); and lower extremities (40%). Each quadrant also was scored for the severity of erythema (E), infiltration (I) and desquamation (D), using a four point scale, in 15 which 0=no symptoms present; 1=slight symptoms; 2=moderate symptoms; 3=striking symptoms; 4=exceptionally striking symptoms. Using a 6-point scale, each region was scored also for the percent of total area that was involved in the psoriatic manifestations of the disease, wherein 0=no involvement; 1=<10% involvement; 2=10-<30% involvement; 3=30-<50% involvement; 4=50-<70% involvement; 5=70-<90% 20 involvement; 6=90-100% involvement. PASI scores were calculated according to the formula given below, in which E=severity score for erythema, I=severity score for infiltration, D=severity score for desquamation and A=total area involved. In this formula, the letters "h," "t," "u" and "l" represent, respectively, the scores in each of the four body regions, i.e., head, trunk, upper extremities and lower extremities. The PASI 25 score varies in steps of 0.1 units from 0.0 (no psoriatic lesions at all) to 72.0 (complete erythroderma of the severest possible degree).

$$\text{PASI} = 0.1(\text{Eh} + \text{Ih} + \text{Dh})\text{Ah} + 0.3(\text{Et} + \text{It} + \text{Dt})\text{At} + 0.2(\text{Eu} + \text{Iu} + \text{Du})\text{Au} + 0.4(\text{El} + \text{Il} + \text{Dl})\text{Al}$$

A secondary endpoint used for the psoriatic aspect of psoriatic arthritis was the Target Lesion Assessment Score. This score was determined for a single target lesion 30 that was selected to be monitored throughout the trial. This measurement is a composite of four different evaluations: 1) plaque evaluation; 2) scaling; 3) erythema; and 4) target lesion response to treatment. The following scale was used for the plaque elevation: 0=none (no evidence of plaque above normal skin level); 1=mild (slight but definite elevation above normal skin level); 2=moderate (moderate elevation with rounded or 35 sloped edges to plaque); 3=severe (hard, marked elevation with sharp edges to plaque); 4=very severe (very marked elevation with very hard sharp edges to plaque). For the scaling assessment: 0=none (no scaling on the lesion); 1=mild (mainly fine scales, with

5 some of the lesion at least partially covered); 2=moderate (somewhat coarser scales, most  
of the lesion at least partially covered); 3=severe (coarse, thick scales, virtually all the  
lesion covered, rough surface); 4=very severe (very coarse thick scales, all the lesions  
covered, very rough surface). For the erythema evaluation: 0=none (no erythema);  
1=mild (light red coloration); 2=moderate (red coloration); 3=severe (very red  
10 coloration); 4=very severe (extreme red coloration). For target lesion response to  
treatment score: 0=completely cleared; 1=almost cleared (~90% improvement);  
2=marked response (~75% improvement); 3=moderate response (~50% improvement);  
4=slight response (~25% improvement); 5=condition unchanged; 6=condition worsened.  
The patient's Target Lesion Assessment Score was determined by summing the plaque,  
15 scaling, erythema and target lesion response scores for the monitored lesion. If the  
monitored lesion worsened, the percentage change from baseline was recorded as a  
negative number.

Treatment and placebo groups were compared in accord with the measurements  
described above, as well as for demographic and background characteristics; premature  
20 discontinuation rate; pain medication requirements; toxicities; serious adverse events;  
side effects reported by patients; number of weeks on drug until subjects met criteria for  
improvement, and response according to PsA subtype. Results were analyzed using  
standard statistical methods.

#### Dosing regimen

25 Recombinant human TNFR:Fc (etanercept) from Immunex Corporation was used  
in this study. The gene fragments encoding the etanercept polypeptides were expressed in  
a Chinese hamster ovary (CHO) expression vector.

TNFR:Fc was supplied as a sterile lyophilized powder containing 10 mg or 25 mg  
TNFR:Fc; 40 mg mannitol, USP; 10 mg sucrose, NF; and 1.2 mg tromethamine (TRIS),  
30 USP per vial. Patients received either a dose of 25 mg of etanercept or a placebo. Vials  
of etanercept or identically-appearing placebo were reconstituted by aseptic injection of  
1.0 mL Bacteriostatic Water for Injection, USP, (containing 0.9% benzyl alcohol), and  
was not filtered during preparation or prior to administration. If storage was required, the  
reconstituted solutions were stored at 2-8°C (36-46°F) in the original vial or in a plastic  
35 syringe for a period of no longer than 28 days. Dose was not changed during the study.  
Study drug was given twice weekly at approximately the same time of day.

5 Results

Study drug was well tolerated in all patients, and adverse events were consistent with this population and were equally distributed among both treatment groups. As illustrated in Tables 1-4, etanercept induced a significant improvement as compared with the placebo group in Psoriatic Arthritis Response (Table 1), ACR20 (Table 2), ACR50 (Table 3), PASI score, 50% improvement (Table 4), PASI score, 75% improvement (Table 5) and improvement in Target Lesion Assessment Score (Table 6). The fractions shown in Tables 1-5 represent numbers of patients. For example, the first entry in Table 1, which is "4/30," indicates that 4 of 30 patients in the placebo group scored as "improved" according to the Psoriatic Arthritis Response measurements. The tables include P-values for the differences between the two study groups, the groups being labeled as "PLACEBO" and "TNFR:Fc." All of the tables include data calculated after the first four weeks of the open label extension portion of the study ("EXTENSION"), during which *all* of the patients in both study groups received etanercept.

Table 1 shows the number of patients in each treatment group who scored as "improved" according to the Psoriatic Arthritis Response scoring system described above. By four weeks, there was a highly significant difference between etanercept and placebo groups. Moreover, after being switched to etanercept during the extension, those patients who had received placebo during the blinded portion of the study were seen to exhibit an improvement over baseline (Table 1, Placebo, EXTENSION). These results indicate that etanercept acts rapidly to alleviate many aspects of psoriatic arthritis.

5

Table 1. Psoriatic Arthritis Response

	<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	4/30 (13%)	23/30 (77%)	0.000
8 weeks	7/30 (23%)	25/30 (83%)	0.000
12 weeks	6/30 (20%)	26/30 (87%)	0.000
EXTENSION	17/23 (74%)	21/25 (84%)	0.356

10 Tables 2 and 3, respectively, illustrate the study results for the ACR20 and ACR50 endpoints. For either measure, a significant difference between etanercept and placebo groups was observed at all three time points during the blinded portion of the study. Given the differences between test and placebo groups after only four weeks of treatment (P=0.000 for ACR20 and P=0.011 for ACR50), these data suggest that notable improvement in ACR scores occurred within the etanercept group very soon after treatment was initiated, possibly after a single dose of etanercept. During the 4 week extension period, during which *all* of the patients received etanercept, a striking improvement in both ACR20 and ACR50 was seen in those patients who had received placebo during the first 12 weeks (Tables 2 and 3).

Table 2. ACR20 Response

	<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	1/30 ( 3%)	18/30 (60%)	0.000
8 weeks	3/30 (10%)	19/30 (63%)	0.000
12 weeks	4/30 (13%)	22/30 (73%)	0.000
EXTENSION	11/23 (48%)	18/25 (72%)	0.093

5

Table 3. ACR50 Response

	<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	0/30 ( 0%)	6/30 (20%)	0.011
8 weeks	1/30 ( 3%)	11/30 (37%)	0.001
12 weeks	1/30 ( 3%)	15/30 (50%)	0.000
EXTENSION	7/23 (30%)	11/25 (44%)	0.316

10 The results of the psoriasis evaluations are presented in Tables 4-6. Tables 4 and 5, respectively, present the numbers and percentages of patients in each group who exhibited a 50% or 75% improvement in PASI score, while Table 6 presents Target Lesion Assessment scores, these latter being denoted as percent improvement over baseline. The data in Tables 4-6 clearly indicate that etanercept induced an improvement in psoriasis for a large percentage of the patients who received it. When single lesions were evaluated (Table 6), the improvement in psoriasis was even more apparent than 15 when PASI scores were used (Tables 4 and 5). It is notable also that, for either PASI scores (Tables 4 and 5) or Psoriasis Target Lesion Assessment Score (Table 6), the scores of the placebo group improved after these patients were switched to etanercept during the extension.

20 Though not shown in Table 6, Target Lesion Assessment Scores for patients who were concurrently receiving methotrexate (14 of the 30 patients in the etanercept group, and 14 patients in the placebo group) were compared with the scores of those patients who did not take methotrexate. Little difference in this index was noted between the patients who received methotrexate and those who did not receive it.

25 Table 4. PASI Score – 50% Improvement

	<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	0/19 ( 0%)	4/19 (21%)	0.037
8 weeks	1/19 ( 5%)	7/19 (37%)	0.019
12 weeks	4/19 ( 21%)	8/19 (42%)	0.165
EXTENSION	6/16 (38%)	6/15 (40%)	0.856

5

Table 5. PASI Response Rate 75% Improvement

	<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	0/19 ( 0%)	1/19 ( 5%)	0.264
8 weeks	0/19 ( 0%)	2/19 (11%)	0.153
12 weeks	0/19 ( 0%)	4/19 (21%)	0.037
EXTENSION	1/16 ( 6%)	4/15 (27%)	0.113

10

Table 6. Psoriasis Target Lesion Assessment  
(Percent Improvement or Worsening Compared with Baseline)

		<u>Placebo</u>	<u>TNFR:Fc</u>	<u>P-value</u>
4 weeks	Mean (SD)	2.7 (27.6)	21.2 (35.2)	0.120
	Median	0.0	14.3	
	MIN--MAX	-50.0 -50.0	-33.3 -100.0	
	N	19	19	
8 weeks	Mean (SD)	-7.5 (25.3)	28.5 (34.1)	0.003
	Median	0.0	29.2	
	MIN--MAX	-50.0 -20.0	-33.3 -100.0	
	N	17	18	
12 weeks	Mean (SD)	9.5 (23.2)	45.7 (31.6)	0.001
	Median	0.0	50.0	
	MIN--MAX	-25.0 -50.0	-16.7 -100.0	
	N	16	19	
EXTENSION	Mean (SD)	28.9 (41.2)	47.1 (35.8)	0.263
	Median	36.7	50.0	
	MIN--MAX	-100.0 -66.7	-33.3 -100.0	
	N	16	15	